

Consent to clinical research – adequately voluntary or substantially influenced?

Sarah Hewlett University of Bristol

Abstract

In clinical research the giving of consent by the patient often lies within the context of illness or the doctor/patient relationship. On exploration of these issues it would appear unlikely that the patient's consent is free of substantial influences, some of which may be strong enough to be controlling.

Five categories of consent are suggested: voluntary, involuntary, coerced, enforced and partially voluntary. It is argued that consent in clinical research is substantially influenced and thus only partially voluntary. Several practical strategies are proposed to ensure adequately voluntary consent by reducing some circumstantial influences when consent to clinical research is obtained.

Introduction

Clinical research is necessary to establish the safety and efficacy of a therapy. It may include, for example, the testing of nursing or physiotherapy techniques, as well as the testing of new drugs, the focus of this paper.

Clinical testing of a new drug is required by the Medicines Control Agency (MCA) before a product licence for that drug can be given. As the drug is being tested for safety and efficacy, patients taking part will be put at risk of unknown side-effects and may also be randomised to receive either the unproven drug or a placebo. When we enter a patient into such a clinical trial we are normally testing a drug appropriate to his or her condition. However, because of randomisation we may not always be selecting a particular drug for a particular patient's needs. If the comparator drug is a placebo then we may not be acting in that patient's best interests. In some cases the patient is being used as a means to an end: establishing the safety and efficacy of a new drug for the benefit of future patients. The justification for this is that the only way to establish the most effective and safe treatments to improve health (desired by most members of society) is by clinical research.¹ By consenting, the patient

knowingly agrees to this goal and makes it his own, becoming an active participant in the research so that it cannot then be said that the patient is being used as a means to an end. Clearly the quality of that consent is therefore vital.

What does clinical research mean for the patient?

The scientific gold standard for clinical research is the randomised controlled trial (RCT) which attempts to establish statistically the risk/benefit ratio of the drug by reducing bias and controlling for variables.² This it does by controlling the selection of well-characterised groups of patients, randomising them into treatment groups, using standardised outcome measurements performed by blinded assessors, and stipulating a population size powerful enough to answer the question being asked. Although not without criticism³ the RCT is a credible test of safety and efficacy within the medical world and some would say it would be unethical to introduce a new drug without RCT data.⁴

Patients participating in an RCT will usually need to attend hospital regularly for safety and efficacy assessments – perhaps clinical examination, blood and urine samples, and possibly X-rays. Such visits may take several hours and their frequency varies from every few days to every month, as does the duration of the RCT (from a few days to several years). Neither the safety nor the efficacy of the drug is yet proven and in addition the patient may receive a placebo during the course of the study. When taken together these are not inconsiderable inconveniences for the patient and although hopefully kept to minimum impact, there is sometimes an element of risk.

How can we protect the patient in an RCT?

Patients participating in clinical research are protected by the requirement for a Clinical Trials Exemption Certificate from the MCA; the Declaration of Helsinki guidelines on the ethical conduct of the research⁵; Research Ethics Committee

Key words

Consent; voluntary; clinical research

approval which must be obtained beforehand⁶; Guidelines on Good Clinical Practice developed by the Association of British Pharmaceuticals Industry and now adopted as an EC directive⁷; peer review by publication (including details of ethics committee approval); public accountability through public access to medical journals, media reports etc, and finally the personal and professional codes of the researchers. By far the strongest protection however, is consent.

The purpose of consent

Clinical research contains an unquantified risk of harm for the patient, it may also involve the use of a placebo and/or a drug which is not fully licensed, and the patient's treatment is randomly allocated: the patient is being used as a means to an end. However, the principle of respect for persons requires that we respect the wishes of others and have concern for their welfare.⁸ Consent is an autonomous authorisation by one person to permit another person to carry out an agreed procedure which affects the subject and therefore by asking patients to consent to research, we respect their wishes, enable them to be self-governing and uphold the principle of respect for persons. In clinical research consent is vital in maintaining trust in the doctor/patient relationship and preventing the patient from being deceived.

What is consent?

Four elements must be present for consent to be morally acceptable: competence, information, understanding of that information, and voluntariness.⁹ Beauchamp and Childress suggest that a person is *competent* "if and only if that person can make reasonable decisions based on rational reasons".¹⁰ Competency however, is a complex issue and is not the focus of this paper, in which we address voluntary consent to clinical research by the competent patient. *Information* must be sufficient and unbiased, such that a substantially autonomous decision can be made. Consent can rarely be fully informed but this does not mean it is not adequately informed.¹¹ For example, I might buy a car based on adequate information about its history and performance, rather than full information about the workings of its engine which I would not understand. Similarly, whilst it is not possible fully to inform patients about the pharmacological actions of the research drug it may be possible adequately to inform them. The manner in which information is provided will also influence adequacy of understanding and it is the responsibility of the health care professional to ensure the patient *understands* the proposed research.¹² This can be done by using appropriate terminology – presented in an unbiased manner – encouraging questions, and ascertaining what the patient understands. These

first three elements of consent have been widely researched and debated but little work has been performed on the fourth element *voluntariness* which is, I propose, seriously threatened in clinical research.

Voluntariness

All decisions are made within the context and influence of people or circumstances. Thus it would be difficult (if not impossible) to define the notion of "fully voluntary" consent. There would always be arguments that further efforts could be made to reduce influences. As with competence, information and understanding the issue is whether voluntariness is adequate. Beauchamp and Childress describe voluntariness as being independent of controlling influences exerted by others and discuss coercion (the intentional use of a credible threat), manipulation (of information to influence a decision) and persuasion (convincing by presenting rational reasons).¹³ This model depends largely on the intentional actions of others. It fails to address the influence of circumstances, which I believe is common in consent to clinical research and which poses an easily overlooked threat to voluntariness. For consent to research to be adequately voluntary two factors must be fulfilled: the absence of controlling influences and the ability to choose either one of at least two options.

Influences or controlling influences?

Whilst circumstances and people will always influence any decision we make, it is the responsibility of the researcher to ensure that in clinical research, these are not so strong as to be controlling. Unlike healthy volunteers, many patients invited to participate in clinical research will have an illness and the experience of illness (which may at times include pain, disability, fear of deterioration or death, physical or emotional dependence)¹⁴ and the accompanying psychological response (possibly depression, mourning, denial, anger, anxiety, passivity and regression to an invalid role)¹⁵ may well reduce autonomy. In addition, a request to enter a research trial may of necessity come at the time of, or soon after, the shock of diagnosis. Furthermore, some patients in hospital feel vulnerable – unaware of the normal routine or what is expected of them, and reduced, as they are, to wearing night-clothes. Is it possible to make a reflective decision, free of strong influences in such a situation?

The doctor/patient relationship is centred around patients' trust that doctors act in their best interests. Thus even though the doctor has explained that treatment in the research trial is randomised and according to a strict protocol, patients often still believe that the doctor will only act in their best interests. In a recent trial 41% of patients believed there were no risks in a phase II trial of a new anti-inflammatory

agent, despite being told it was unlicensed and being tested for safety.¹⁶ So strong is this trust that patients may agree to anything the doctor suggests and even the invitation to participate may be viewed as a recommendation rather than a request. Patients may feel flattered by the request and under an obligation to help because of past care received.

For many patients the relationship is an unequal one, with the doctor being perceived as a powerful figure on whom they depend, making it difficult for them to take an unnaturally dominant role and refuse the doctor's request. Patients may fear that if they do so, the doctor will be displeased and their future care will be jeopardised. Patients may view clinical research as a means of access to care (which may be true for patients in countries where many people do not have health care insurance) and may also equate the frequent safety visits with improved care.

External pressures may be brought to bear on the patient: the patient may be asked to decide immediately, without time to reflect; family and friends may suggest the patient "ought" to participate; the facts we give the patient will be laden with our beliefs; we may use closed questions or statistics which are loaded in a persuasive fashion (for example 75% of patients do well rather than 25% do badly); doctors may be under pressure to reach target numbers, with academic and financial kudos resulting from a completed trial. Thus the influences on the patient are multiple and complex.

Theoretical options or realistic options?

Is it possible that the option of consenting or not consenting to clinical research may be theoretical rather than realistic? For example, there is currently no effective treatment for AIDS and so an invitation to test a potential therapeutic agent will be the only means of access to the only possible alternative to death. Whilst the purist might suggest that this patient does still have a choice, in the real world I believe few patients would find death a realistic option. Patients invited to participate in clinical research may be limited by practical difficulties. In a draft research proposal, general practices were to be randomised to particular treatments for osteoarthritis (OA) as specific arms of a research trial. As standardised treatment regimens in different practices were being compared, all OA patients from each GP would be treated in this new manner. A patient has the choice of declining the research, but if this is the only treatment his GP can now offer, does he have any real option? This initial proposal has now been extensively revised after these issues were raised.

These two illustrations offer different examples of how options can be limited. For the patient with AIDS this is by circumstance but for the patient with OA, the initial trial design itself limited his options.

Most choices in life are limited in some way but where those limits are imposed by others then the quality of the consent, being deliberately constrained, may be morally unacceptable.

We have looked at influences on the patient and limitations of options, but in practice are these strong enough to make it difficult for the patient to refuse consent? Refusal rates are low, with none at all in recent years in a neighbouring unit (personal communication) and in our own unit, in one study only four out of 28 patients refused.¹⁶ We compared these four patients who declined to enter a phase III trial of a specific anti-rheumatoid drug ("refusers") with 17 patients who consented to take part in a similar Phase II trial ("consenters"). The consenters rated how difficult it would have been for them to say "no" if they had wanted to refuse and the refusers rated how difficult it actually was (10 cm visual analogue scale [VAS], very easy to very difficult). There was a significant difference between the consenters' median score (0.9, range 0–5.4) and the refusers' (7.15, range 5.2–9.6) ($p=0.0036$, Mann Whitney U test).¹⁶ Therefore, assuming this to be a reasonable representation of patients invited to take part in drug trials, we must appreciate that patients experience considerable difficulties when it comes to refusing the doctor's request, such that their consent may not be adequately voluntary.

What is consent if it isn't voluntary?

I propose that there are a number of situations in which consent is not adequately voluntary and may or may not be acceptable.¹⁷ As a simple illustration let us assume that I wish to purchase a jacket and have sufficient funds to buy either red jacket A or green jacket B. If I decide to buy jacket A because I like the way I look in it then this would be a reflective decision, free of constraints or coercive pressures – an adequately *voluntary* choice. However, if I had a compulsion to wear green I might automatically choose jacket B. This reflex action which I could not control would be an *involuntary* choice. Third, suppose my employer had insisted that all staff should wear red jackets and that non-compliant staff would be sacked then my subsequent decision to buy red jacket A would have been *coerced by the action of others*. However, if I had lost £10 on the way to the shop and had to buy jacket B because it was all that I could afford, then my choice would have been *enforced by circumstances*. There is however, still a form of consent which fits none of these categories. Suppose a friend who accompanies me declares that jacket A suits me best and is of a better quality. This opinion, coming from someone I respect, leads me to decide to buy jacket A. Such a choice is not voluntary but neither is it involuntary, coerced by use of a credible threat; nor is it enforced by circumstances. But it is not free from pressure (however well-intentioned) and has been substantially influenced. I

would suggest that such a decision is partially voluntary.

Should consent to clinical research also be thought of as partially voluntary? It is rarely involuntary, coerced or enforced but as I have shown there are many potential influences on the patient. Whilst some pressures may be subtle and not strong enough to enforce or coerce consent, it is quite possible that a combination of the factors described may substantially influence consent so as to make it only partially voluntary. We may have to accept that much consent in clinical research is partially (and possibly adequately) voluntary, just as it is partially but adequately informed.

The point at which influences cease to be substantial but become sufficiently controlling as to make consent morally unacceptable may vary from person to person but there are ways in which we can and should try to reduce those influences or make the patient aware of them.

Reducing influences on consent to clinical research

Whilst it could be argued that the adequately autonomous patient is the best person to decide if his or her decision is adequately voluntary, as health care professionals we have a professional responsibility to try and promote adequately voluntary consent by the manner in which we obtain it. This is similar to our responsibilities in trying to ensure adequately informed consent by the manner in which we inform patients. Areas where influences could be reduced include the doctor/patient relationship, selection of patients, education of the researcher and information given during recruitment.

The doctor/patient relationship

Interventions here might allow the patient to step back from the relationship and consider the proposal in a more detached manner. This could be done by using a researcher/doctor as well as a carer/doctor, by using a patient advocate or by recruiting patients in groups. Separating the doctors into researcher/doctors and carer/doctors¹⁸ may allow patients to feel less anxious about future care if they refuse. However, the doctors are likely to be, or to become, close colleagues; the carer/doctor will have to be responsible for recruitment, which involves him in the research; the researcher/doctor will need to know about the patient's care; and both doctors will need to deal with clinical problems as they arise, thus causing practical problems to arise as a result of creating this split. In therapeutic research, care and research are so closely interlinked that it is impractical and impossible not to mix the two.

A patient advocate might ask questions on the patients' behalf, act as an impartial sounding board,

and deter the doctor from pressurising or hurrying the patient. A lay advocate (friend or relative) might not be able to interpret technical details any better than the patient, might also be in awe of the perceived power of the doctor, and might influence the patient by the strength of their own relationship. A non-doctor health care professional might be well suited to advocacy because of his or her familiarity with the health care system, rapport with patients and ability to interpret technical data. However, such a professional may be seen as part of the doctor's team and may well be employed by the doctor so that he or she has a vested interest in encouraging recruitment. However, a trained advocate, perhaps funded by the health authority or trust, could be specifically trained and supervised by the research ethics committee. Such posts, separate from any research or care team, have the potential to develop into an independent advocacy system.

Talking to patients about clinical research in groups rather than individually may reduce pressure on patients – more outspoken patients may ask questions which others are reluctant to voice. However, patients may also find it difficult to go against the group decision if they do not agree with it.

Selection of patients

It has been suggested that we should first approach patients who are best able to understand the research, and who are most highly motivated and least captive, such as health care professionals who have the particular disease in question.¹⁹ The numbers in this group are likely to be so small as to make research impractical and where there is a link between educational level and disease, selecting highly educated subjects might bias the study.

Education of researchers

Education of health care professionals in research ethics and obtaining consent should ease pressure on patients by increasing the researchers' awareness. This is gradually happening as nursing and medical schools include medical ethics in their curricula.

Information to patients

Specific trial information sheets are vital and patients must have time to read and discuss them. However, as they are written by the researchers who wish the patient to consent there is the real possibility that they will be biased. Consumers for Ethics in Research (CERES) produce a standard leaflet on medical research which is not written in relation to specific projects.²⁰ Having seen this leaflet and following our own research into consent, we have developed a Patient's Guide to Medical Research (figure 1) which is given to all rheumatology patients as they are invited to participate in clinical research,

alongside the specific trial information sheets.²¹ It is independent of any single researcher or research trial, is designed to cover many of the issues raised in this article and has an “easy” readability level.²²

We have made other changes to the consent process, including giving the responsibility for information-giving and initial interview and consent to the research nurses, who are perhaps seen as less powerful figures than the doctor. We give patients at least 48 hours to reflect on the proposal and encourage them to discuss it with family, friends and GP, before telephoning them to discuss the trial, answer questions and take their decision, which is passed on to the doctor on their behalf. We believe that these strategies reduce the difficulty patients experience in declining to take part in research and we will be assessing this in future trials.

Conclusion

Voluntary consent to clinical research may be compromised because of the circumstances under which it must be obtained and the idea that consent must be either voluntary or not voluntary is too naive a concept in this situation. I have argued that consent, which requires two realistic options and freedom from controlling influences, may be voluntary, involuntary, coerced by others, enforced by circumstances or substantially influenced (partially voluntary). Consent by patients in clinical research must often be only partially voluntary, because it lies within the context of illness or the doctor/patient relationship. The duty of health care professionals is to ensure that partially voluntary consent is adequately voluntary, just as we do for information in consent. I have proposed several routes to reduce influences on voluntariness, the most promising of which appear to be the use of health care professionals initially, the use of an advocate (who should be trained, independent and employed through the research ethics committee), well-educated researchers, time for the patient to reflect and the use of an independent guide to research. Such moves are very necessary if we are to ensure adequately voluntary consent in clinical research. As Jonas argues, the consequences of ruthless research may be far-reaching:

“Let us remember that a slower progress in the conquest of diseases would not threaten society, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having”.²³

Acknowledgements

The author would like to acknowledge the support of Miss Louise de Raeve and Dr Don Evans (Centre

for Philosophy and Health Care, University College of Swansea) and Professor Paul Dieppe and Dr John Kirwan (University of Bristol Rheumatology Unit).

Sarah Hewlett, MA, RGN, RM, is Clinical Research Manager in the Rheumatology Unit at Bristol Royal Infirmary.

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Figure 1

PATIENT'S GUIDE TO MEDICAL RESEARCH

Your doctor has invited you to take part in medical research. This leaflet may help you make your decision.

What is medical research?

Medical research is a way of finding out about illnesses, such as what causes them. It can also be a way of testing different or new treatments, such as new tablets. Your doctor will explain the aim of this study and what it involves.

Who looks after my interests?

The hospital has a Research Ethics Committee (made up of doctors, nurses and members of the public) which must approve all medical research. It looks at every research study to make sure that it is fair (or ethical) in the way it treats patients. Only when it has given permission can the study start. As well as this, if a doctor wants to test a new tablet or medicine they must get permission from a Government Committee. This Committee makes sure that the trial tablet has had reasonable safety checks, before giving the doctor permission to use it. During the study your doctor will look after your interests and continue to give you the best possible care. If the doctor is not happy with your condition during the research you will be asked to stop the study.

Do I have to say yes?

No. Taking part in medical research is voluntary. Your doctor will not think badly of you if you say no. You do not have to give a reason if you say no. Your doctor will continue to care for you whatever you decide. If you say yes at first, you can still leave the study later on if you change your mind.

What do patients think about taking part?

Some patients take part because they feel they have a duty to help medical progress. Others believe it will help their own illness and some see it as a way of helping other people. On the other hand, some patients decide *not* to take part because they believe research should not involve patients or because they feel it is risky or inconvenient. All these feelings are understandable and reasonable.

However, some patients feel *obliged* to take part because of the care they have received or because they feel the doctor will not look after them in the future if they say no. Others are simply too embarrassed to say no. Feelings like this must not affect your decision.

This leaflet contains questions which you should discuss with the doctor who invited you to take part. The doctor will not mind answering your questions at all. *You must make the decision which is right for you.* You cannot do that unless you find out as much as you can about what is involved.

Before you make a decision about taking part, we suggest you ask the doctor the following questions

1 What is the aim of the research?

Is it to test a new treatment or to follow the course of my illness? Why does it need to be done?

2 What will I be asked to do?

Will I be asked to take tablets? Will I have to stop my usual tablets? Will I have to come up for blood tests or X-rays? How often? How long will the study last?

Ask as much as you can and find out what taking part means. Your doctor should give you an information sheet to take home.

3 What are the benefits or risks for me if I take part?

Ask how the research might help you. Often the aim is not to benefit you, but to help future patients. Do you mind this?

Ask your doctor if there are any risks in taking part. Don't sit and worry about possible side-effects – ask!

Extra questions to ask if you are invited to test a medicine

4 How will my treatment be decided?

Several treatments may be tested and to make sure the study is not biased, one of the trial treatments may be given to you by chance, not by your doctor's decision. Would you mind?

5 Will I get a dummy treatment?

Some studies compare one treatment with a dummy treatment, called a placebo. Ask your doctor if there is a chance you might be given a placebo. How would you feel about that?

6 If this is a new medicine am I insured if things go wrong?

You should check with your doctor. The Research Ethics Committee has also asked this question.

7 Could I have standard treatment instead?

Ask about the standard treatments that are available to you if you decide not to take part in the research study.

If there is time, you may like to discuss the study with your family or your General Practitioner.

When you have all the facts you can make your decision without feeling under any pressure

Thank you for thinking about our medical research. We hope this leaflet has helped you reach the decision that is right for you.

Produced by Sarah Hewlett, Research Sister, University of Bristol and United Bristol Healthcare Trust. 1993